Role of hypogonadism in development of bone alterations in thalassemic patients

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Summary

Although transfusions and chelation therapy have improved survival of patients afflicted with Thalassemia Major (TM), endocrine alterations are still common complications. Particularly, hypogonadism plays an important role in the aetiology of osteoporosis in these patients. It is clear that in most patients the gonadal failure is a consequence of a pituitary damage and that a hypogonadotropic hypogonadism occurs; nevertheless, also a gonadal damage because of iron deposition may be a further cause of hypogonadism. Prevalence of the pubertal failure ranges between 50 to 80% of the cases. In some studies ferritin levels have been correlated with hypogonadism, suggesting that improvement of chelation treatments may prevent or reduce the appearance of hypogonadism in TM patients. Treatment with HRT has shown conflicting results, but patients who started the treatment in young age present better results than those who started later. However we may conclude that HRT is an important treatment option but should be prescribed in early age and associated with biphosphonates.

KEY WORDS: thalassemia, hypogonadism, osteoporosis, iron overload.

Beta thalassemia major (TM) is an important health concern in many countries, mostly in the Mediterranean area, in the Middle East, India, East Asia. In 1988 a report from the WHO documented that almost 50000 children per year were born with TM.
In the last decades, improved programs of transfusional and chelation therapy have permitted to TM patients to survive until their forties or fifties and to get a better quality of life (1). However, several complications progressively arise and in particular endocrine alterations are common with diabetes, hypothyroidism, hypoparathyroidism, and hypogonadism being well known complications of adult thalassemia major (2-4).
More recently, in adult TM patients, bone mass deficiency has been recognised as a major problem that may cause pathologic fractures and limb deformities and greatly worsen the quality of life of these patients (5, 6). The etiology of bone mass deficiency in thalassemia is still unclear and many factors have been suggested as possible causes, including IGF-I deficiency, low vitamin D levels, alterations of genes related to collagen synthesis, bone cortical thinning because of bone marrow expansion and altered levels of some oligoelements such as zinc and copper (7). However, a main role is probably played by hypogonadism that is a hallmark of adult TM patients.
In this brief review, we will examine the characteristics of hypogonadism in TM patients and the possible link between hypogonadism and bone mass deficiency. Finally, we will discuss the role of the hormonal substitutive therapy in the prevention and treatment of bone mass deficiency in TM.

Prevalence and characteristics of gonadal failure in thalassemia major

Most TM patients present a delayed or absent puberty. In the patients who present puberty (at normal or late age), a gonadal failure often progressively occurs with appearance of menstrual disorders and anovulation in women and spermatic abnormalities and reduced sexual activity in males. While it was initially suggested that a primary gonadal deficiency (a hypergonadotropic hypogonadism) occurs in TM patients, it is now clear that in most patients the gonadal failure is a consequence of a pituitary damage and that a hypogonadotropic hypogonadism occurs. Primitive gonadal damage may also occur but appears generally later (sometimes also in patients with hypogonadotropic hypogonadism). Therefore, in some adult TM patients (generally after the third decade) a mixed hypogonadism (central and gonadal) may be present (8).
All studies have documented that the prevalence of hypogonadism in adult TM patients is very high. In an Italian multicentric study, failure of the puberty was observed in 51% of the male and in 47% of female subjects. Between the female patients who reached a normal menarche, 23% presented a secondary amenorrhea and 11.6% oligomenorrhea (9).
In an Iranian study, puberty was delayed or absent in 72.6% of females and 80.8 % of the males and a disturbance of gonadal function was the most common endocrinopathy.
Several years ago, we have shown that about 70% of adult TM patients (both males and females) present some degree of hypogonadism (19). More recently, studying 30 adult TM women (mean age 28.5 ± 1.3 years), we found that TM patients had lower serum levels of LH, FSH and estradiol (Figure 1) than controls of similar age (10). A 80% prevalence of hypogonadotropic hypogonadism was found and 20% of patients with hypogonadotropic hypogonadism presented also some evidence of primary gonadal failure.
A subset of adult TM patients present normal gonadal function. In our study, six adult TM women had normal ovulatory cycles with normal circulating levels of LH, FSH, estradiol and progesterone. Two of these TM patients previously had spontaneous successful pregnancies. Therefore, while most TM patients progressively develop a sexual hormone deficiency, some remain eugonadal. It is unclear what mechanism may determine these differences. In fact, while it is possible that differences in chelation or transfusional programs may explain it, we did not find any evidence of it and serum ferritin levels were not significantly different in eugonadal compared to hypogonadic adult TM women.

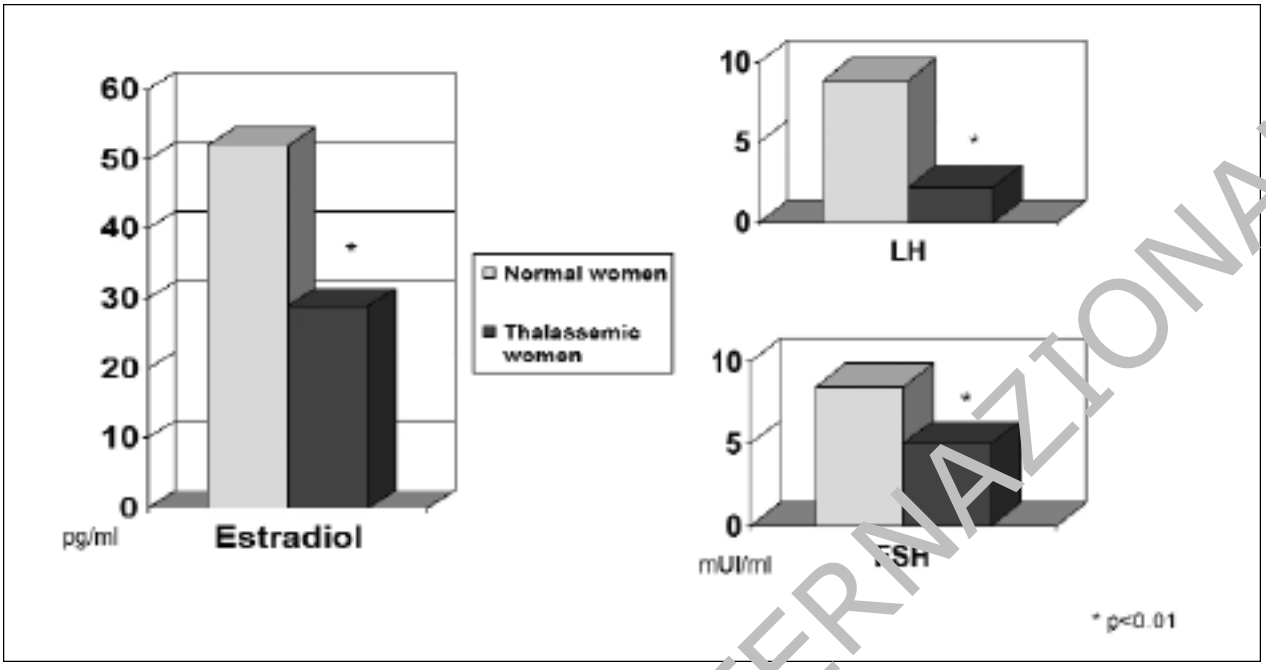

Figure 1 - Serum FSH, LH and estradiol in normal and in thalassemic adult patients.

Causes of hypogonadism in adult TM patients

It has been suggested that in TM patients the hypothalamus and the pituitary are damaged by the iron overload (11). In fact the pituitary gland is very sensitive to iron and also a modest deposition may impair its functionality. Histological studies have confirmed the damage of the pituitary gland by iron overload in TM patients (12) and MRI has shown a significantly smaller anterior pituitary volume (13). Other studies have shown that iron overload may also directly damage the gonads (14). Therefore, it may be assumed that the hypogonadism of adult TM patients is mainly a consequence of the iron deposit.
Some authors have reported higher ferritin levels in subjects who had hypogonadism compared to those with normal gonadal function (15). Ferritin is the protein that stores iron intracellularly and when its capability is exceeded an excess of active iron is released and catalyses the formation of free radicals. Free radicals may damage membrane lipids, leading to mitochondrial and lysosomal damage and finally to cell death. Because of these findings it has been suggested that improvement of chelation treatments may prevent or reduce the appearance of hypogonadism in TM patients (16). While it may be probable, other studies did not find such correlations and our normogonadic patients had the same transfusion and chelation treatment than hypogonadic patients. Moreover, while hypogonadic patients had slightly higher ferritin circulating levels, the difference with normogonadic patients was not significant.

Relationships between hypogonadism and bone mass deficiency in TM

It is well known that sexual hormone deficiency determines an alteration of bone metabolism with increased bone resorption and progressive evolution towards osteoporosis. While most studies have been conducted in menopausal women, it is clear, from clinical and experimental data, that sexual hormone deficiency may determine osteopenia or osteoporosis at any age and in both sexes. Because of it and although many other possible causes are present in thalassemia, hypogonadism may have a main role in determining bone mass deficiency.
Consistent with this hypothesis, we have shown that in adult TM patients a direct correlation between low bone mass and reduced estradiol exists, suggesting that reduced bone mass in many TM patients is mostly dependent on sex hormone deficiency (10). Moreover, hypogonadic TM patients had lower L1-L4 z score (Figure 2) and higher levels of bone markers (Figure 3) than eugonadal TM patients. All these data confirm that gonadal failure plays a main role in inducing bone mass deficiency of adult TM patients.

HRT effects on bone mass deficiency

Because this important role of hypogonadism, we should expect that hormonal replacement therapy (HRT) corrects or prevents bone mass deficiency in adult TM patients. Conflicting results have been presented with some studies indicating a clear improvement and other giving doubtful results. In our recent study, we found that female TM patients treated with HRT still have reduced bone mass and increased bone turnover compared to normal women of similar age. However, patients who started the HRT in younger age had better results than patients who started the treatment later. Maybe, it is important to start the treatment early, at the pubertal age. On the other hand, it cannot be excluded that HRT is not sufficient because other factors contribute to the bone mass deficiency of TM patients. Consistent with our results, Lasco et al. found that bone mass, measured by DEXA, was lower in all TM patients than in controls, but the difference was more marked in patients who didn't receive HRT (17). We can conclude that HRT is an important

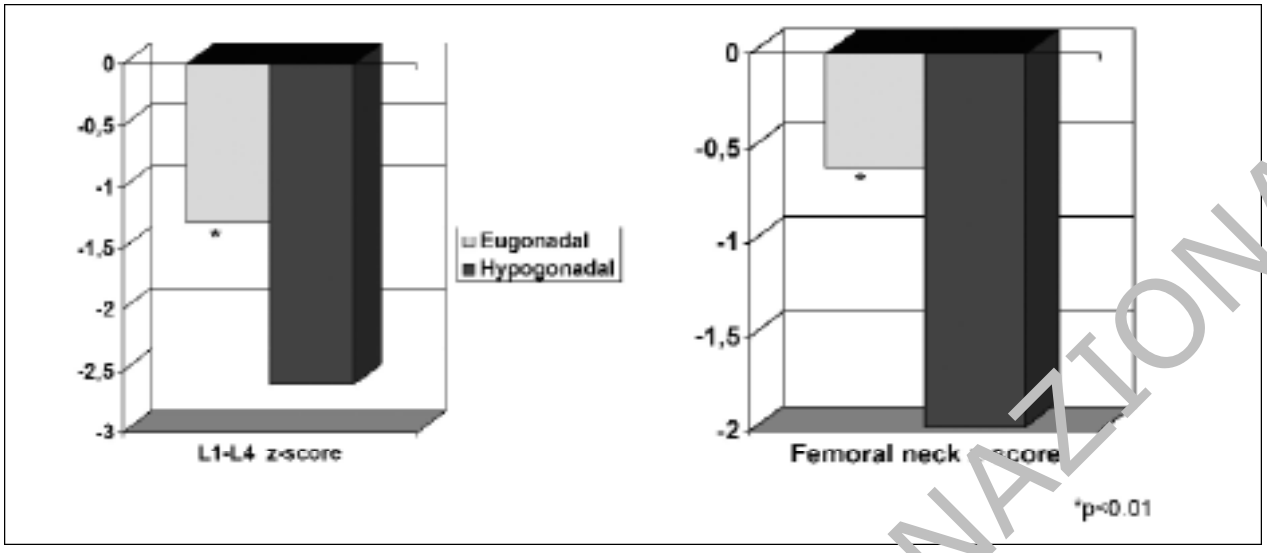

Figure 2 - Z score differences between eugonadal and hypogonadal thalassemic patients.

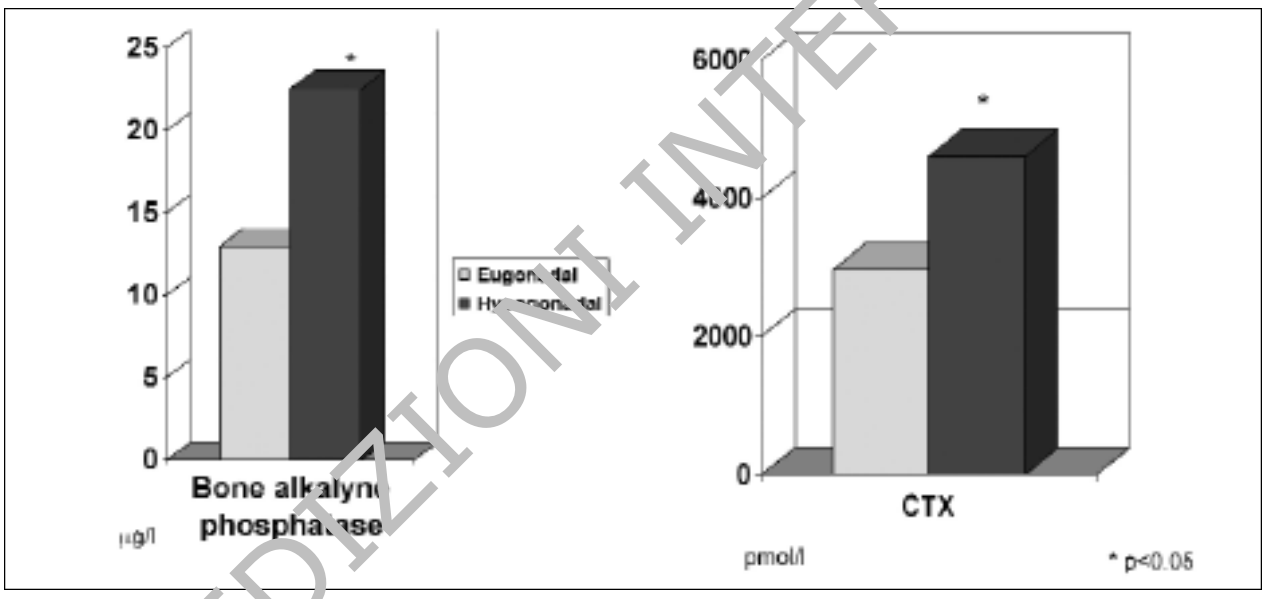

Figure 3 - Difference in bone alkaline phosphatase and CTX between eugonadal and hypogonadal thalassemic patients.

part of the treatment of bone mass deficiency in adult TM patients but that the treatment has to be started early and that often alone is not sufficient to normalize bone mass.
Because of the disappointing results of HRT on bone mass in adult TM patients, it has been suggested to associate HRT and bisphosphonates (18). Limited experience is available but the results of our group and of other authors suggest that the results may be better than with HRT alone.

Conclusions

Hypogonadism is very common in adult TM patients and may be present in about 80% of the patients. It is important to assess hypothalamic-pituitary-gonadal function in young women with beta thalassemia major, so that those with gonadal failure may start as soon as possible the replacement therapy. Patients with normal gonadal function should re-evaluate periodically their sexual hormone function because hypogonadism may develop after puberty and involve both pituitary and the gonads. In patients who do not respond adequately to HRT, other possible causes of osteoporosis should be screened and bisphosphonates could be added to the substitution therapy.

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